REMARKS

The Official Action of October 15, 2007, made final, and The Advisory Action of January 31, 2008, and the references cited therein have been carefully considered. The Applicant respectfully requests reconsideration of the application in view of the following remarks. Consistent with Applicants' response transmitted January 15, 2008, which was not entered purusant to the Advisory Action mailed January 31, 2008, Applicants' amendments are being submitted to ensure their entry. Claim 16 has been amended to incorporate Claim 17 and Claim 17 has been canceled.

Claims 15, 16, 18-27 are pending in the application.

Rejection of Claims 15-27 for Obviousness over Dorn et al. (U.S. Patent No. 5,719,147)

Claims 15-27 stand rejected under 35 U.S.C. § 103(a) as being obvious over Dorn et al. (U.S. Patent No. 5,719,147). The Applicants respectfully traverse this rejection and provide the following comments.

The Applicants respectfully assert that U.S. Patent No. 5,719,147 does not disclose or suggest the claimed invention. Nor would U.S. Patent No. 5,719,147 have motivated or enabled one skilled in the art to prepare the subject compounds in accordance with the claimed invention. The Examiner has failed to demonstrate the specific motivation in U.S. Patent No. 5,719,147 that would have motivated one of ordinary skill in the art to prepare and utilize the subject compound in accordance with the claimed invention. The Examiner has failed to establish a prima facie case of obviousness. Even if the Examiner has established a prima facie case of obviousness, the present invention provides unexpected results relative to the disclosure of U.S. Patent No. 5,719,147.

U.S. Patent No. 5,719,147 discloses at Example 75, column 104, processes for obtaining the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine starting from:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine, by using the procedure of Example 70, column 102, wherein:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine is reacted with:

N-methylcarboxy-2-chloro-acetamidrazone, and

N,N-diisopropylethylamine in acetonitrile at room temperature for 20 hours, to give:

2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine, which is:

heated in xylenes at reflux for 2 hours.

The process disclosed in U.S. Patent No. 5,719,147 is very different from the presently claimed process.

As more fully recited in the claims, the claimed process for obtaining the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine ["aprepitant"] comprises:

reacting the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine with:

N-methylcarboxy-2-chloro-acetamidrazone, and

an inorganic base in toluene, optionally in the presence of a specified solvent, to give:

2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine, which is, optionally washed with an aqueous phase, then:

cyclized at a temperature of 140-150°C.

As the Examiner acknowledges, U.S. Patent No. 5,719,14 does not teach any of the following reaction conditions:

(1) the temperature of the cyclization process;

(2) the use of the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine;

(3) the use of toluene;

(4) the use of an inorganic base (such as potassium carbonate);

(5) the use of a specified solvent (such as dimethylsulfoxide or dimethylformamide); or

(6) the use of an aqueous wash, such as with an aqueous salt solution, prior to conducting the cyclization.

Applicants respectively submit that there would have been no motivation nor guidance in U.S. Patent No. 5,719,147 for one of ordinary skill in the art to have conducted the subject process in accordance with the claimed invention. The Examiner has not provided a reasonable factual basis to support the assertion that one of ordinary skill in the art whould have

been motivated by U.S. Patent No. 5,719,147 to have conducted the subject process in accordance with the claimed invention.

Applicants respectfully request that the Examiner to consider the claimed process in its entirety, including each and every element of the claimed process, as well as how each and every element relates to all of the other elements in the claimed process to prepare the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine.

The Examiner mistakenly relies on inapplicable disclosures in U.S. Patent No. 5,719,147 to assert that U.S. Patent No. 5,719,147 taken as a whole would have provided teaching and/or direction and motivation for each of the claimed reaction steps.

There is not teaching whatsoever in U.S. Patent No. 5,719,147 that the conditions employed for such diverse chemical processes to prepare or purify structurally different compounds should be employed in the context of each of the claimed reaction steps to prepare the desired compound 5[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy]-(S)-(4-fluorophenyl)-4-morpholinyl]-methyl]1,2-dihydro-3h-1,2,4-triazol-3-one in accordance with the claimed process.

(1) The Temperature of the Cyclization Process:

There would have been no motivation in U.S. Patent No. 5,719,147 to have conducted the cyclization process at a temperature of about 140-150°C. Example 75 indicates that 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine was prepared by heating 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-N-methylcarboxyacetamidraxono)morpholine in 15 ml a mixture of xylenes at reflux for 2 hours. The CRC Handbook of Chemistry and Physics indicates that the boiling point of o-xylene is 144°C, the boiling point of m-xylene is 139°C, and the boiling point of p-xylene is 138°C. There is no indication that the process conditions in Example 75 of heating at reflux in a mixture of xylenes would have actually corresponded to a temperature of 140-150°C and, alternatively, there would have been no direction regarding how the temperature should have been changed.

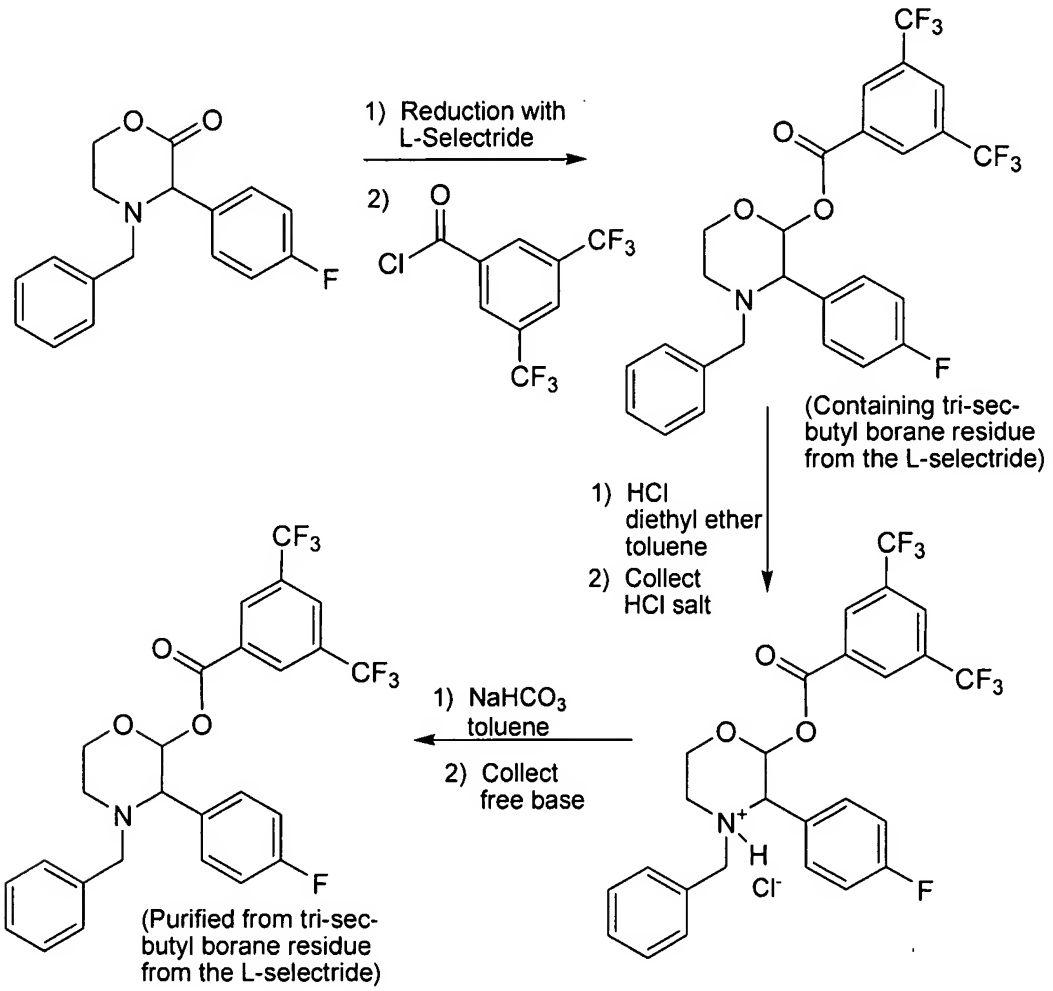
(2) The Use of the Hydrochloride Salt of 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine:

There would have been no motivation in U.S. Patent No. 5,719,147 to have used the hydrochloride salt of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine. In fact, Example 75 of U.S. Patent No. 5,719,147 teaches away from the present invention by indicating that the free base of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine should be employed.

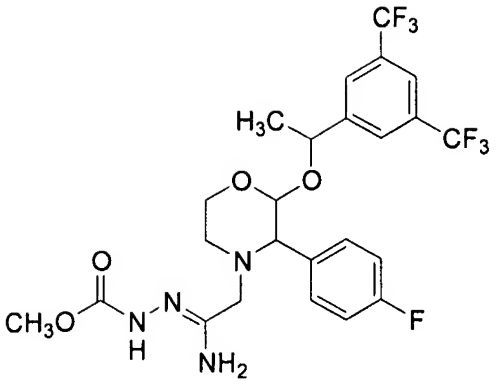
Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 101, column 131, are not relevant to the process conditions of the present claims. Example 75, column 104, is certainly the more relevant disclosure.

Example 101 discloses that 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester was prepared by reduction of the free base of (S)-3-(4-flurophenyl)-4-(phenylmethyl)-2-morpholinone with L-selectride. The hydrochloride salt of the final product 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester is expressly stated as having been prepared from the free base crude product to remove tri-sec-butyl borane residue (from the L-Selectride reduction) from the crude product and purify the final product, not in the context of an alkylation reaction such as the claimed process.

For the convenience of the Examiner, Applicants have attempted to graphically depict the reactions disclosed by Example 101:



The process step of Example 101 to purify a crude product by making a hydrochloride salt from the free base of the product, isolating the hydrochloride salt and then breaking the hydrochloride salt of the product back to the free base (i.e. last step in the process) is very different from the claimed invention which uses a hydrochloride salt as the starting material for a the reaction with N-methylcarboxy-2-chloro-acetamidrazone (i.e. first step in the process) to give the compound of formula 4:



4

The teachings of Example 101 provide no guidance whatsoever with respect to any alkylation reaction, let alone the claimed process. Example 101 teaches simply a purification process (i.e. prepare the hydrochloride salt of a crude free base, isolate the hydrochloride salt away from reagent by-products, break the hydrochloride salt back to the free base, then isolate the purified free base).

Accordingly, the process conditions noted by the Examiner that are disclosed in Example 101, column 131, to purify the product 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester following its prepartion are not relevant to the claimed cyclization process which employ the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine as the starting material.

Example 75 of U.S. Patent No. 5,719,147 is in fact more relevant than Example 101 because it teaches away from the present invention by indicating that the free base of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine should be employed for the alkylation reaction.

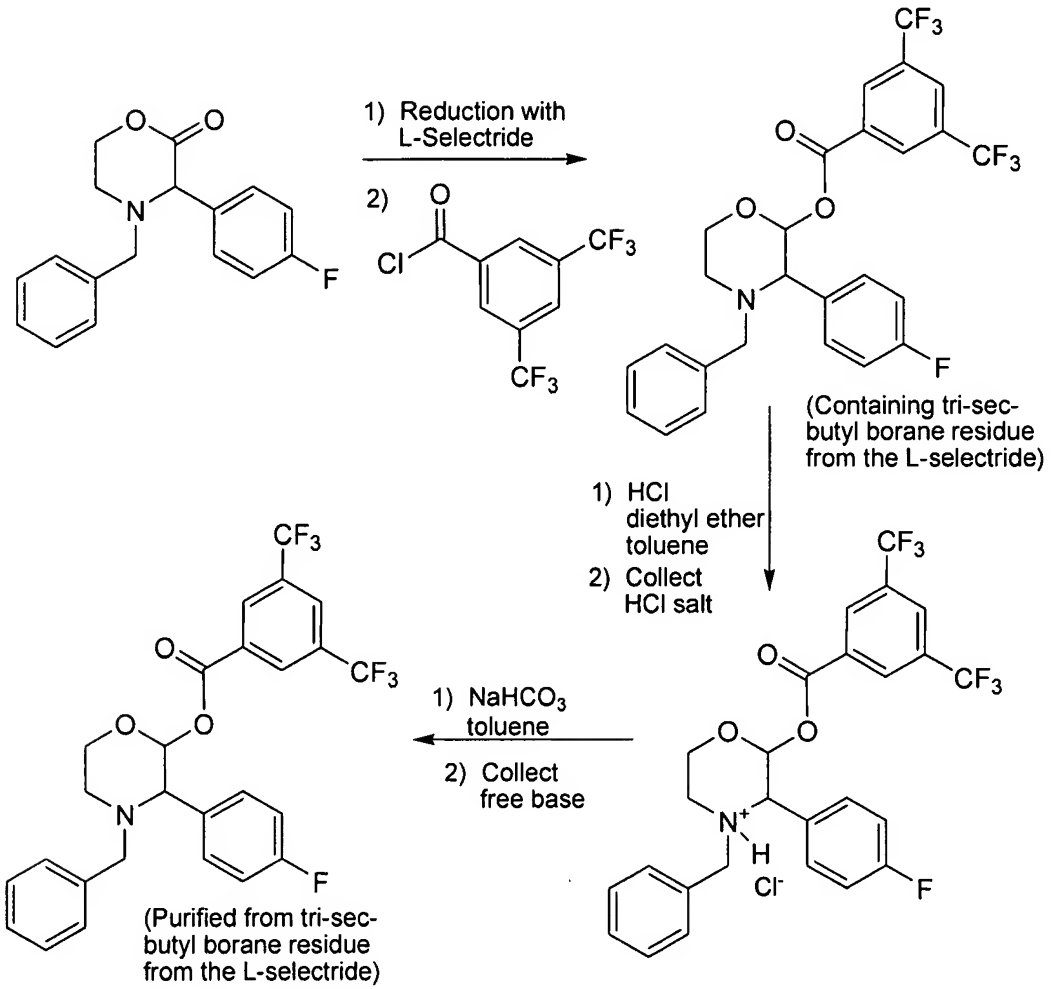
(3) The Use of Toluene

There would have been no motivation in U.S. Patent No. 5,719,147 to use toluene, rather than xylene. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the solvent xylene would have been required.

Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 101, column 131, are not relevant to the process conditions of the present claims.

Example 101 discloses that 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester was prepared by reduction of the free base of (S)-3-(4-flurophenyl)-4-(phenylmethyl)-2-morpholinone with L-selectride. The final product 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester was purified to remove tri-sec-butyl borane residue (from the L-Selectride reduction) by making the hydrochloride salt from the crude free base, isolating the hydrochloride salt, then breaking the hydrochloride salt back to the free base with a slurry of aqueous sodium bicarbonate and toluene.

The reactions disclosed by Example 101 are again depicted for the convenience of the Examiner:



The process step of Example 101 to purify a crude product by making a hydrochloride salt from the free base, isolating the hydrochloride salt and then breaking the hydrochloride salt of the product back to the free base with aqueous sodium bicarbonate and toluene (i.e. last step in the process) is very different from the claimed invention which uses toluene as a solvent in a the reaction mixturel for the reaction of the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine with N-methylcarboxy-2-chloro-acetamidrazone to give the compound of formula 4 (i.e. first step in the process).

The teachings of Example 101 provide no guidance whatsoever with respect to any alkylation reaction, let alone the claimed process. Example 101 teaches simply a purification

process (i.e. prepare the hydrochloride salt of a crude free base, isolate the hydrochloride salt away from reagent by-products, break the hydrochloride salt back to the free base with aqueous sodium bicarbonate and toluene, then isolate the purified free base).

Accordingly, the process conditions noted by the Examiner that are disclosed in Example 101, column 131, to purify the product 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester following its prepartion are not relevant to the claimed cyclization process which employ the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine as the starting material.

Example 75 of U.S. Patent No. 5,719,147 is in fact more relevant than Example 101 because it teaches away from the present invention by indicating that xylenes should be employed as the reaction solvent for the alkylation reaction.

(4) The Use of An Inorganic Base

There would have been no motivation in U.S. Patent No. 5,719,147 to use an inorganic base, rather than the organic base N,N-diisopropylethylamine. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the organic base N,N-diisopropylethylamine should have been employed.

In this regard, Applicants respectfully submit that one of ordinary skill in the art would have considered N,N-diisopropylethylamine [i.e. $NH(CH(CH_3)_2)_2$] to be an organic base, and not an inorganic base as stated by the Examiner.

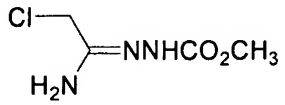
Example 75 discloses the use of N,N-diisopropylethylamine in acetonitrile to prepare 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine. Applicants respectfully submit that N,N-diisopropylethylamine would have been considered by one of ordinary skill to be an organic base, and not an inorganic base.

Applicants respectfully submit that the listing of bases referenced by the Examiner on column 65 is not relevant to the process conditions of the present claims because this disclosure relates the first step of Scheme 6 which is the formation of a trifluoromethanesulfonate ester (triflate) of the appropriate benzyl alcohol, not alkylation of an amine.

Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 83, column 107, are not relevant to the process conditions of the present claims.

Example 83 discloses the alkylation of a morpholine starting material with N,N-diacetyl-4-bromomethyl-2-imidazolone.

In contrast, the present claims relate to reaction of the starting material with N-methylcarboxy-2-chloro-acetamidrazone:



3

Accordingly, the process conditions noted by the Examiner that are disclosed in Example 83, column 107, to prepare a substituted methyl imidazolone are not relevant to the claimed cyclization process to prepare a N-methylcarboxy-2-acetamidrazone intermediate.

Example 75 of U.S. Patent No. 5,719,147 is in fact more relevant than Example 83 because it teaches away from the present invention which uses an inorganic base by indicating that the organic base N,N-diisopropylethylamine should be employed for the alkylation reaction.

(5) The Use of Specific Solvents

There would have been no motivation in U.S. Patent No. 5,719,147 to use a specific solvent which is selected from dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, acetonitrile, N,N-dimethylacetamide and hexamethylphosphoramide, rather than acetonitrile. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the acetonitrile would have been required.

Example 75 discloses the use of N,N-diisopropylethylamine in acetonitrile to prepare 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine.

Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 83, column 107, are not relevant to the process conditions of the present claims.

Example 83 discloses the alkylation of a morpholine starting material with N,N-diacetyl-4-bromomethyl-2-imidazolone to prepare 2-(SR)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(4-(2-oxo-1,3-imidazolo)methylmorpholine directly.

In contrast, the present claims relate to reaction of the starting material with N-methylcarboxy-2-chloro-acetamidrazone to prepare 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)-morpholinee, which is subsequently cyclized to form the (5-oxo-1,2,4-triazolo) ring.

Accordingly, the process conditions noted by the Examiner that are disclosed in Example 83, column 107, to prepare a substituted methyl imidazolone are not relevant to the claimed cyclization process to prepare a N-methylcarboxy-2-acetamidrazone intermediate.

(6) The Use of An Aqueous Wash

There would have been no motivation in U.S. Patent No. 5,719,147 to use an aqueous wash, such as with an aqueous salt solution, prior to conducting the cyclization.

Applicants respectfully submit that the process conditions referenced by the Examiner that are disclosed in Example 101, column 131, are not relevant to the process conditions of the present claims.

Example 101 discloses that 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester was prepared by reduction of the free base of (S)-3-(4-flurophenyl)-4-(phenylmethyl)-2-morpholinone with L-selectride. The final product 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester was purified to remove tri-sec-butyl borane residue (from the L-Selectride reduction) by making the hydrochloride salt from the crude free base, isolating the hydrochloride salt, then breaking the hydrochloride salt back to the free base with a slurry of aqueous sodium bicarbonate and toluene.

The process step of Example 101 to purify a crude product by making a hydrochloride salt from the free base, isolating the hydrochloride salt and then breaking the hydrochloride salt of the product back to the free base with aqueous sodium bicarbonate and toluene is very different from the claimed invention which uses an aqueous wash prior to conducting the cyclization step.

The teachings of Example 101 provide no guidance whatsoever with respect to any alkylation reaction, let alone the claimed process. Example 101 teaches simply a purification process (i.e. prepare the hydrochloride salt of a crude free base, isolate the hydrochloride salt away from reagent by-products, break the hydrochloride salt back to the free base with aqueous sodium bicarbonate and toluene, then isolate the purified free base).

Accordingly, the process conditions noted by the Examiner that are disclosed in Example 101, column 131, to purify the final product 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester following its prepartion are not relevant to the claimed cyclization process which employ an aqueous wash prior to conducting the cyclization step.

Even if one of ordinary skill in the art had been motivated to alter the process disclosed in U.S. Patent No. 5,719,147, there would have been no direction in U.S. Patent No. 5,719,147 regarding which specific reagents, solvents, temperature, additional steps and/or other conditions should have been employed in the process. The Examiner mistakenly relies on inapplicable disclosures in U.S. Patent No. 5,719,147 to assert that U.S. Patent No. 5,719,147 taken as a whole would have provided teaching and/or direction and motivation for the particular conditions employed in each of the claimed reaction steps

Accordingly, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness.

Unexpected Results

As previously submitted, even if the Examiner has established a prima facie case of obviousness, the present invention provides unexpected results relative to the disclosure of U.S. Patent No. 5,719,147. As noted in the specification (page 1, lines 14-19), the present invention provides a more practical and economical method for preparing the desired compound. As noted in the specification (page 7, lines 12-13), the present invention further provides an efficient process for

preparing the desired compound that also minimizes the use of toxic solvents. Surprisingly, the present invention also gives the desired compound in 85% yield (page 8, lines 8-9), which is unexpectedly higher than the yield disclosed for the procedure in U.S. Patent No. 5,719,147 (79% yield) (Example 75, column 104).

Applicants respectfully submit that they have provided a showing that such results were greater than those which would have been expected from the prior art to an unobvious extent and that the results are of a significant, practical advantage.

By actual numerical advantage the claimed process provides the desired compound in 85% yield which is higher than the 79% yield disclosed in the prior art. This numerical advantage is particularly advantageous in the context of large-scale synthesis of the desired pharmaceutical product. In addition, the claimed process provides a more efficient process for preparing the desired compound by reducing the number of manipulations and steps relative to the process disclosed in the prior art. In addition, the claimed process provides a more environmentally-friendly process for preparing the desired compound by minimizing the use of toxic solvents relative to the process disclosed in the prior art.

Accordingly, Applicants respectfully submit that the rejection of Claims 15-27 under 35 U.S.C. § 103(a) as being obviousness over Dorn et al. (U.S. Patent No. 5,719,147) is untenable and should be withdrawn.

Applicants respectfully contend that the application is allowable and a favorable response from the Examiner is earnestly solicited.

Respectfully submitted,

By _____

J. Eric Thies
Reg. No. 35,382
Attorney for Applicant

MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-3904

Date: February 15, 2008